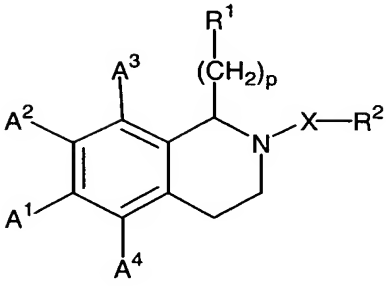
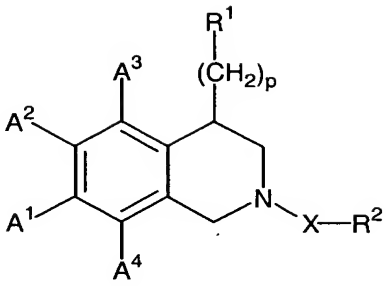
CLAIMS

1. A compound of the formula:



or



(I) (II)

wherein:

A^1 is hydrogen, hydroxy, (C_1-C_4)alkoxy, or (C_1-C_4)alkanoyloxy, said (C_1-C_4)alkoxy or said (C_1-C_4)alkanoyloxy being optionally substituted by hydroxy, halo, or a partially saturated, fully saturated, or fully unsaturated five to twelve membered ring optionally having up to four heteroatoms independently selected from oxygen, sulfur, and nitrogen, or A^1 is R^3-(C_1-C_4)alkoxy wherein R^3 is pyrrolidino, piperidino, morpholino, or dimethylamino;

A^2, A^3, and A^4 are independently selected from hydrogen, hydroxy, (C_1-C_4)alkoxy, and halo;

R^1 is phenyl; pyridyl; piperidinyl; (C_1-C_7)alkyl; adamantyl; a partially saturated, fully saturated, or fully unsaturated three to twelve membered ring optionally having up to four heteroatoms selected independently from oxygen, sulfur, and nitrogen; a bicyclic ring consisting of two fused independently partially saturated, fully saturated, or fully unsaturated five to six membered rings, wherein said bicyclic ring includes up to four heteroatoms independently selected from oxygen, sulfur, and nitrogen; or a bicyclic ring system consisting of two rings joined by a covalent bond, said rings being independently partially saturated, fully saturated, or fully unsaturated three to eight membered rings, wherein said bicyclic ring system includes up to four heteroatoms independently selected from oxygen, sulfur, and nitrogen; wherein each of the above R^1 groups is optionally substituted with up to seven fluoro atoms, or with up to three substituents independently selected from Group A, wherein Group A consists of hydroxy, halo, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_3-

C_8)cycloalkyl, R^3-(C_1-C_4)alkoxy, (C_2-C_4)alkenyl-$COOR^7$ wherein R^7 is hydrogen or (C_1-C_4)alkyl, (C_0-C_4)alkyl-$COOR^7$, (C_1-C_4)alkanoyloxy-(C_2-C_4)alkenyl, (C_2-C_4)alkenyl-$CONR^4R^5$ wherein R^4 and R^5 are independently hydrogen, (C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy-(C_1-C_4)alkylene, or (C_3-C_8)cycloalkyl, or R^4 and R^5 taken together with the nitrogen atom to which they are attached form pyrrolidino, piperidino, morpholino, or hexamethyleneimino, (C_0-C_4)alkyl-$CONR^4R^5$, (C_0-C_4)alkyl-NR^4R^5, $OCH_2CH_2NR^8R^9$ wherein R^8 and R^9 are independently methyl or ethyl, or R^8 and R^9 taken together with the nitrogen atom to which they are attached form pyrrolidino, piperidino, morpholino, or hexamethyleneimino, propyl-R^8R^9, and SO_2-R^6 wherein R^6 is imidazolyl, thienyl, benzathienyl, or isoxazyl, optionally substituted with up to three substituents independently selected from (C_1-C_4)alkyl;

X is a covalent bond, $(CH_2)_n$ where n is 1, 2, or 3, (C_0-C_1)alkylene-phenylene-(C_0-C_1)alkylene, CO_2, (C_0-C_3)alkylene-CO-(C_0-C_3)alkylene, or (C_0-C_4)alkylene-SO_2-(C_0-C_4)alkylene;

R^2 is (C_1-C_9)alkyl; (C_2-C_4)alkenyl; benzhydryl; a partially saturated, fully saturated, or fully unsaturated three to eight membered ring optionally having up to four heteroatoms selected independently from oxygen, sulfur, and nitrogen; a bicyclic ring consisting of two fused independently partially saturated, fully saturated, or fully unsaturated five to six membered rings, wherein said bicyclic ring includes up to four heteroatoms independently selected from oxygen, sulfur, and nitrogen; or a bicyclic ring system consisting of two rings joined by a covalent bond, said rings being independently partially saturated, fully saturated, or fully unsaturated three to eight membered rings, wherein said bicyclic ring system includes up to four heteroatoms independently selected from oxygen, sulfur, and nitrogen; wherein said (C_1-C_9)alkyl is optionally substituted with one to seven fluoro substituents, or up to three substituents independently selected from Group B, wherein Group B consists of chloro, (C_1-C_4)alkoxy, amino, and (C_1-C_4)alkylcarbonyl; wherein said (C_2-C_4)alkenyl is optionally substituted with up to three substituents independently selected from Group C, wherein Group C consists of halo, (C_1-C_4)alkoxy, amino, and (C_1-C_4)alkylcarbonyl; and wherein said benzhydryl, said 5 to 8 membered ring, said bicyclic ring, and said bicyclic ring system is

optionally substituted with up to three substituents independently selected from Group D, wherein Group D consists of halo, hydroxy, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, imidazolyl, amino, (C_1-C_4)alkylcarbonylamino, and (C_1-C_4)alkylcarbonyl; and

p is 0, 1, or 2;

with the proviso that

when X is $(CH_2)_2$ or $(CH_2)_3$, p is 0, and R^1 is phenyl or phenyl substituted with a single chloro, fluoro, bromo, hydroxy, methoxy, pyrrolidinoethoxy, piperidinoethoxy, or morpholinoethoxy substituent, then R^2 is not phenyl, methoxyphenyl, tert-butyl, or cyclopentyl;

when X is CH_2, $(CH_2)_2$, $COCH_2$, or CH_2CO, A^1 is hydrogen, and R^1 is phenyl, then R^2 is not phenyl; and

when X is a covalent bond, p is 0, A^1 is hydrogen or methoxy, and R^1 is phenyl or phenyl substituted with a single chloro, fluoro, bromo, methoxy, pyrrolidinoethoxy, or piperidinoethoxy substituent, then R^2 is not phenyl or *m*-fluorophenyl.

2. A compound of claim 1 wherein:

A^1 is hydroxy;

A^2, A^3, and A^4 are hydrogen; and

p is 0.

3. A compound of claim 1 wherein R^1 is phenyl, pyridyl, (C_1-C_4)alkyl, adamantyl, naphthyl, or a partially saturated, fully saturated, or fully unsaturated five to six membered ring optionally having up to two heteroatoms selected independently from oxygen, sulfur, and nitrogen; wherein each of said R^1 groups is optionally substituted with up to seven fluoro atoms, or with up to three substituents independently selected from Group A.

4. A compound of claim 3 wherein R^1 is phenyl, cyclohexyl, pyridyl, thienyl, isopropyl, or adamantyl; wherein each of said R^1 groups is optionally substituted with up to seven fluoro atoms, or with up to three substituents independently selected from Group A.

5. A compound of claim 4 wherein R^1 is phenyl or cyclohexyl; wherein each of said R^1 groups is optionally substituted with up to seven fluoro atoms, or with up to three substituents independently selected from Group A.

6. A compound of claim 3 wherein each of said R^1 groups is optionally substituted with up to three halo atoms, or with one substituent selected from hydroxy, $(C_1\text{-}C_2)$alkoxy, pyrrolidino-$(C_1\text{-}C_4)$alkoxy, dimethylamino, $(C_2\text{-}C_4)$alkenyl-$COOR^7$, $COOR^7$, $(C_2\text{-}C_4)$alkenyl-$CONR^4R^5$ wherein R^4 and R^5 are independently hydrogen, $(C_1\text{-}C_4)$alkyl, hydroxy$(C_1\text{-}C_4)$alkyl, $-(CH_2CH_2\text{-}O\text{-}CH_3)$, or $(C_5\text{-}C_6)$cycloalkyl, or R^4 and R^5 taken together with the nitrogen atom to which they are attached form piperidino or morpholino, or $SO_2\text{-}R^6$ wherein R^6 is imidazolyl optionally substituted with up to three substituents independently selected from $(C_1\text{-}C_4)$alkyl.

7. A compound of claim 6 wherein each of said R^1 groups is optionally substituted with up to three fluoro atoms, or with one substituent selected from iodo, chloro, bromo, hydroxy, methoxy, pyrrolidino-ethoxy, dimethylamino, $COOR^7$ wherein R^7 is hydrogen or methyl, or ethenyl-$CONR^4R^5$ wherein R^4 and R^5 are both methyl, or R^4 and R^5 taken together with the nitrogen atom to which they are attached form piperidino or morpholino.

8. A compound of claim 7 wherein each of said R^1 groups is optionally substituted with one hydroxy or pyrrolidino-ethoxy.

9. A compound of claim 1 wherein X is a covalent bond, CH_2, CH_2-phenylene, CO_2, CO-$(C_0\text{-}C_2)$alkylene, or $SO_2\text{-}(C_0\text{-}C_2)$alkylene.

10. A compound of claim 1 wherein X is a covalent bond, CO, or SO_2.

11. A compound of claim 1 wherein R^2 is $(C_1\text{-}C_7)$alkyl; propenyl; a partially saturated, fully saturated, or fully unsaturated five to seven membered ring optionally having up to two heteroatoms selected independently from oxygen, sulfur, and nitrogen; a bicyclic ring consisting of two fused independently partially saturated, fully saturated, or fully unsaturated five to six membered rings, wherein said bicyclic ring includes up to two oxygen atoms; or biphenyl; wherein said $(C_1\text{-}C_7)$alkyl is optionally

substituted with one to seven fluoro substituents, or up to three substituents independently selected from Group B; wherein said propenyl is optionally substituted with up to three substituents independently selected from Group C; and wherein each of said 5-7 membered ring, said bicyclic ring, and said biphenyl is optionally substituted with up to three substituents independently selected from Group D.

12. A compound of claim 11 wherein R^2 is methyl, t-butyl, phenyl, cyclohexyl, isoxazolyl, tetrahydropyranyl, naphthyl, or benzodioxolyl; wherein each of said methyl or t-butyl is optionally substituted with one to seven fluoro substituents, or up to three substituents independently selected from Group B; and wherein each of said phenyl, cyclohexyl, isoxazolyl, tetrahydropyranyl, naphthyl, or benzodioxolyl is optionally substituted with up to three substituents independently selected from Group D.

13. A compound of claim 12 wherein R^2 is trifluoromethyl or phenyl; wherein said phenyl is optionally substituted with up to three substituents independently selected from Group D.

14. A compound of claim 11 wherein each of said $(C_1\text{-}C_7)$alkyl and said propenyl is substituted with one to three fluoro substituents, or up to two substituents independently selected from amino and methylcarbonyl; and wherein each of said 5-7 membered ring, said bicyclic ring, and said biphenyl is substituted with up to three fluoro substituents, or up to two substituents independently selected from hydroxy, $(C_1\text{-}C_3)$alkyl, amino, and methylcarbonyl.

15. A compound of claim 1 wherein:

A^1 is hydroxy;

A^2, A^3, and A^4 are hydrogen;

p is 0;

R^1 is phenyl, cyclohexyl, pyridyl, thienyl, isopropyl, or adamantyl; wherein each of said R^1 groups is optionally substituted with up to three fluoro atoms, or with one substituent selected from iodo, chloro, bromo, hydroxy, methoxy, pyrrolidino-ethoxy, dimethylamino, $COOR^7$ wherein R^7 is hydrogen or methyl, or ethenyl-$CONR^4R^5$ wherein R^4 and R^5 are both methyl, or R^4 and

R^5 taken together with the nitrogen atom to which they are attached form piperidino or morpholino;

X is a covalent bond, CH_2, CH_2-phenylene, CO_2, CO-(C_0-C_2)alkylene, or SO_2-(C_0-C_2)alkylene; and

R^2 is methyl, t-butyl, phenyl, cyclohexyl, isoxazolyl, tetrahydropyranyl, naphthyl, or benzodioxolyl; wherein each of said methyl or t-butyl is optionally substituted with one to three fluoro substituents, or up to two substituents independently selected from amino and methylcarbonyl; and wherein each of said phenyl, cyclohexyl, isoxazolyl, tetrahydropyranyl, naphthyl, or benzodioxolyl is optionally substituted with up to three fluoro substituents, or up to two substituents independently selected from hydroxy, (C_1-C_3)alkyl, amino, and methylcarbonyl.

16. A compound of claim 15 wherein R^1 is phenyl or cyclohexyl, each of which is optionally substituted with up to three fluoro atoms, or with one substituent selected from iodo, chloro, bromo, hydroxy, methoxy, pyrrolidino-ethoxy, dimethylamino, $COOR^7$ wherein R^7 is hydrogen or methyl, or ethenyl-$CONR^4R^5$ wherein R^4 and R^5 are both methyl, or R^4 and R^5 taken together with the nitrogen atom to which they are attached form piperidino or morpholino.

17. A compound of claim 15 wherein R^1 is optionally substituted with one hydroxy or pyrrolidino-ethoxy.

18. A compound of claim 15 wherein X is a covalent bond, CO, or SO_2.

19. A compound of claim 15 wherein R^2 is trifluoromethyl or phenyl, wherein said phenyl is optionally substituted with up to three fluoro substituents, or up to two substituents independently selected from hydroxy, (C_1-C_3)alkyl, amino, and methylcarbonyl.

20. A compound of claim 15 wherein:

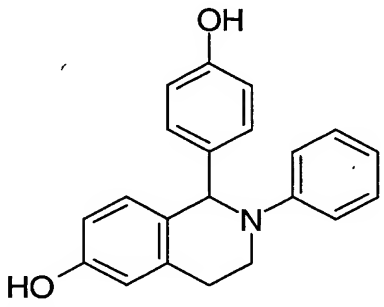
R^1 is phenyl or cyclohexyl, each of which is optionally substituted with one hydroxy or pyrrolidino-ethoxy;

X is a covalent bond, CO, or SO_2; and

R^2 is trifluoromethyl or phenyl; wherein said phenyl is optionally substituted with up to three fluoro substituents, or up to two substituents independently selected from hydroxy, (C_1-C_3)alkyl, amino, and methylcarbonyl.

21. A compound of claim 15 which is

1-(4-hydroxy-phenyl)-2-phenyl-1,2,3,4-tetrahydroisoquinolin-6-ol



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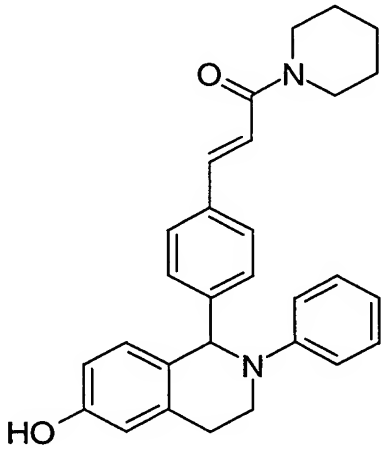
3-[4-(6-hydroxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-phenyl]-1-piperidin-1-yl-propenone



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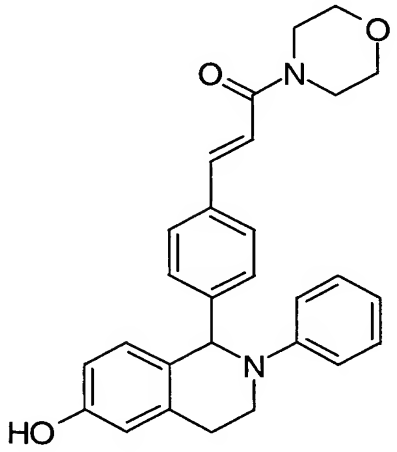
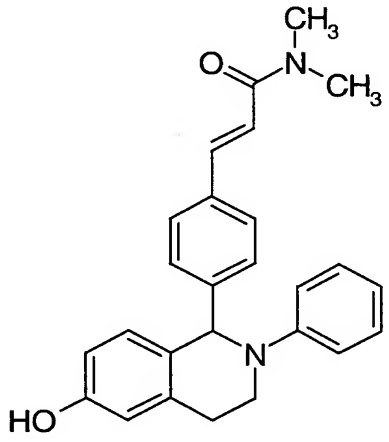
3-[4-(6-hydroxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-phenyl]-1-morpholin-4-yl-propenone

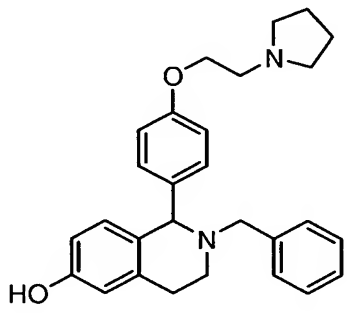


, or

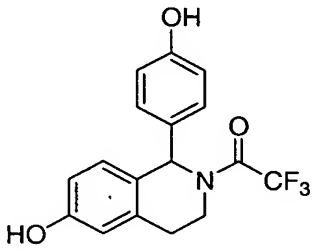
3-[4-(6-hydroxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-phenyl]-N,N-dimethyl-acrylamide



22. A compound of claim 15 which is 2-benzyl-1-[4-(2-pyrrolidin-1-yl-ethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-ol



23. A compound of claim 15 which is 2,2,2-trifluoro-1-[6-hydroxy-1-(4-hydroxyphenyl)-3,4-dihydro-1H-isoquinolin-2-yl]-ethanone



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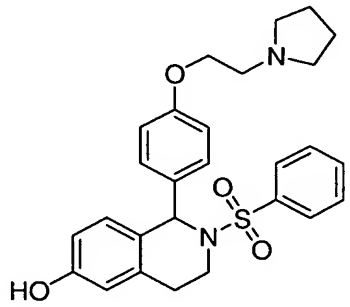
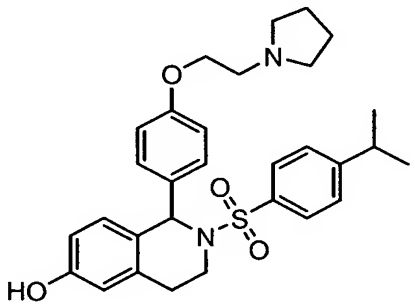
24. A compound of claim 15 which is

2-benzenesulfonyl-1-[4-(2-pyrrolidin-1-yl-ethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-ol



, or

2-(4-isopropylbenzenesulfonyl)-1-[4-(2-pyrrolidin-1-yl-ethoxy)phenyl]-1,2,3,4-tetrahydroisoquinolin-6-ol



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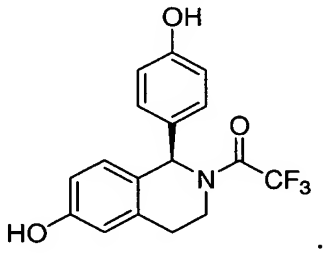
25. A compound of claim 21 which is 1-(4-hydroxy-phenyl)-2-phenyl-1,2,3,4-tetrahydroisoquinolin-6-ol.

26. A compound of claim 21 which is 3-[4-(6-hydroxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-phenyl]-1-piperidin-1-yl-propenone.

27. A compound of claim 21 which is 3-[4-(6-hydroxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-phenyl]-1-morpholin-4-yl-propenone.

28. A compound of claim 21 which is 3-[4-(6-hydroxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-phenyl]-N,N-dimethyl-acrylamide.

29. A compound of claim 23 which is 2,2,2-trifluoro-1-[6-hydroxy-1(R)-(4-hydroxyphenyl)-3,4-dihydro-1H-isoquinolin-2-yl]-ethanone



30. A compound of claim 1 wherein:

said compound is of formula (I);

A^1 is hydroxy, $(C_1\text{-}C_4)$alkoxy, $(C_1\text{-}C_4)$alkanoyloxy, or pyrrolidino-ethoxy;

A^2, A^3, and A^4 are hydrogen;

p is 0 or 1;

R^1 is $(C_1\text{-}C_4)$alkyl, $(C_4\text{-}C_7)$cycloalkyl, adamantyl, phenyl, pyridyl, or thienyl, wherein each of said phenyl, pyridyl, or thienyl groups is optionally substituted with up to three fluoro atoms, or with one substituent selected from iodo, chloro, bromo, hydroxy, methoxy, dimethylamino, $OCH_2CH_2NR^8R^9$, $COOR^7$, ethenyl-$COOR^7$, or ethenyl-$CONR^4R^5$ wherein R^4 and R^5 are both methyl, or R^4 and R^5 taken together with the nitrogen atom to which they are attached form pyrrolidino, piperidino, hexamethyleneimino, or morpholino;

X is a covalent bond, CH_2, CH_2-phenylene, CO_2, CO-$(C_0\text{-}C_2)$alkylene, or SO_2-$(C_0\text{-}C_2)$alkylene; and

R^2 is $(C_1\text{-}C_7)$alkyl, phenyl, benzyl, thienyl, $(C_5\text{-}C_7)$cycloalkyl, isoxazolyl, imidazolyl, tetrahydropyranyl, naphthyl, or benzodioxolyl, wherein said $(C_1\text{-}C_7)$alkyl is optionally substituted with one to three fluoro substituents, or up to two substituents independently selected from amino and methylcarbonyl, and

wherein each of said phenyl, thienyl, (C_5-C_7)cycloalkyl, isoxazolyl, tetrahydropyranyl, naphthyl, and benzodioxolyl is optionally substituted with up to three fluoro substituents, or up to two substituents independently selected from hydroxy, methoxy, (C_1-C_3)alkyl, amino, and methylcarbonyl.

31. A compound of claim 30 wherein:

p is 0;

X is SO_2;

R^1 is not substituted with ethenyl-$COOR^7$;

R^2 is phenyl, benzyl, napthyl, isoxazoyl, (C_5-C_7)cycloalkyl, or (C_1-C_4)alkyl, wherein each of said phenyl, benzyl, napthyl, and isoxazoyl is optionally substituted with up two (C_1-C_3)alkyl groups.

32. A compound of claim 31 wherein R^1 is phenyl or thienyl, each of which is optionally substituted with up to three fluoro atoms or with a single $OCH_2CH_2NR^8R^9$ group.

33. A compound of claim 30 wherein:

p is 0;

X is CO;

R^1 is not substituted with ethenyl-$COOR^7$;

R^2 is (C_5-C_7)cycloalkyl, (C_3-C_7)alkyl, napthyl, or trifluoromethyl, wherein said (C_3-C_7)alkyl is optionally subtituted with up to 3 fluoro atoms.

34. A compound of claim 33 wherein R^1 is phenyl or thienyl, each of which is optionally substituted with up to three fluoro atoms or with a single $OCH_2CH_2NR^8R^9$ group.

35. A compound of claim 30 wherein:

p is 0;

X is CH_2;

R^1 is not substituted with ethenyl-$COOR^7$;

R^2 is phenyl, thienyl, or benzodioxolyl, each of which is optionally substituted with up to 3 fluoro atoms or an imidazoyl group.

36. A compound of claim 35 wherein R^1 is phenyl or thienyl, each of which is optionally substituted with up to three fluoro atoms or with a single $OCH_2CH_2NR^8R^9$ group.

37. A compound of claim 30 wherein:

p is 0;

X is a covalent bond;

R^1 is not substituted with chloro, methoxy, or ethenyl-$COOR^7$;

R^2 is phenyl, thienyl, $(C_5$-$C_7)$cycloalkyl, or tetrahydropyranyl, wherein each of said R^2 groups is optionally substituted with up to two methyl groups, or said phenyl and thienyl groups are optionally substituted with up to 3 fluoro atoms.

38. A compound of claim 30 wherein:

p is 0;

X is CO_2;

R^1 is not substituted with ethenyl-$COOR^7$;

R^2 is phenyl or $(C_1$-$C_4)$alkyl, each of which is optionally subtituted with up to 3 fluoro atoms.

39. A compound of claim 38 wherein R^1 is phenyl or thienyl, each of which is optionally substituted with up to three fluoro atoms or with a single $OCH_2CH_2NR^8R^9$ group.

40. A compound of claim 1 wherein said compound is of formula (II).

41. A compound of claim 40 wherein:

A^1 is hydroxy, $(C_1$-$C_4)$alkoxy, or $(C_1$-$C_4)$alkanoyloxy;

A^2, A^3, and A^4 are hydrogen;

p is 0 or 1;

R^1 is $(C_1$-$C_4)$alkyl, $(C_4$-$C_7)$cycloalkyl, adamantyl, phenyl, pyridyl, or thienyl, wherein each of said phenyl, pyridyl, thienyl, or $(C_5$-$C_7)$cycloalkyl groups is optionally substituted with up to three fluoro atoms, or with one

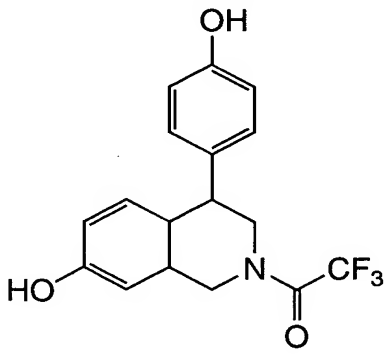
substituent selected from iodo, chloro, bromo, hydroxy, methoxy, dimethylamino, $OCH_2CH_2NR^8R^9$, $COOR^7$, or ethenyl-$CONR^4R^5$ wherein R^4 and R^5 are both methyl, or R^4 and R^5 taken together with the nitrogen atom to which they are attached form pyrrolidino, piperidino, hexamethyleneimino, or morpholino;

X is a covalent bond, CH_2, CH_2-phenylene, CO_2, CO-$(C_0$-$C_2)$alkylene, or SO_2-$(C_0$-$C_2)$alkylene; and

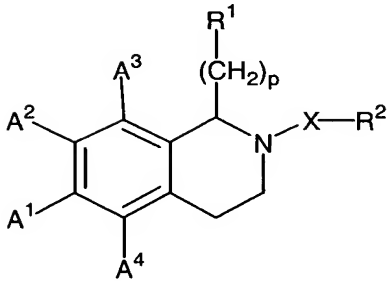
R^2 is $(C_1$-$C_7)$alkyl, phenyl, benzyl, thienyl, $(C_5$-$C_7)$cycloalkyl, isoxazolyl, tetrahydropyranyl, naphthyl, or benzodioxolyl, wherein said $(C_1$-$C_7)$alkyl is optionally substituted with one to three fluoro atoms, or up to two substituents independently selected from amino and methylcarbonyl, and wherein each of said phenyl, thienyl, cyclohexyl, isoxazolyl, tetrahydropyranyl, naphthyl, and benzodioxolyl is optionally substituted with up to three fluoro atoms, or up to two substituents independently selected from hydroxy, methoxy, and $(C_1$-$C_3)$alkyl.

42. A compound of claim 15 wherein said compound is of formula (II).

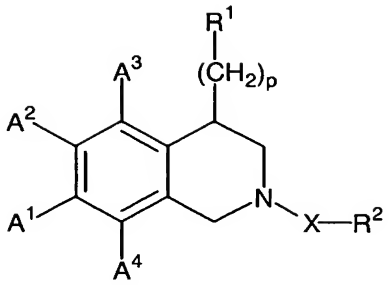
43. A compound of claim 42 which is 2,2,2-trifluoro-1-[7-hydroxy-4-(4-hydroxy-phenyl)-3,4-dihydro-1H-isoquinolin-2-yl]-ethanone



44. A compound of the formula:



or



(I) (II)

wherein:

A^1 is hydrogen, hydroxy, $(C_1$-$C_4)$alkoxy, or $(C_1$-$C_4)$alkanoyloxy, said $(C_1$-$C_4)$alkoxy or said $(C_1$-$C_4)$alkanoyloxy being optionally substituted by hydroxy, halo, or a partially saturated, fully saturated, or fully unsaturated five to twelve membered ring optionally having up to four heteroatoms independently selected from oxygen, sulfur, and nitrogen, or A^1 is R^3-$(C_1$-$C_4)$alkoxy wherein R^3 is pyrrolidino, piperidino, morpholino, or dimethylamino;

A^2, A^3, and A^4 are independently selected from hydrogen, hydroxy, $(C_1$-$C_4)$alkoxy, and halo;

R^1 is phenyl; pyridyl; piperidinyl; $(C_1$-$C_7)$alkyl; adamantyl; a partially saturated, fully saturated, or fully unsaturated three to twelve membered ring optionally having up to four heteroatoms selected independently from oxygen, sulfur, and nitrogen; a bicyclic ring consisting of two fused independently partially saturated, fully saturated, or fully unsaturated five to six membered rings, wherein said bicyclic ring includes up to four heteroatoms independently selected from oxygen, sulfur, and nitrogen; or a bicyclic ring system consisting of two rings joined by a covalent bond, said rings being independently partially saturated, fully saturated, or fully unsaturated three to eight membered rings, wherein said bicyclic ring system includes up to four heteroatoms independently selected from oxygen, sulfur, and nitrogen; wherein each of the above R^1 groups is optionally substituted with up to seven fluoro atoms, or with up to three substituents independently selected from Group A, wherein Group A consists of hydroxy, halo, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, $(C_3$-$C_8)$cycloalkyl, R^3-$(C_1$-$C_4)$alkoxy, $(C_2$-$C_4)$alkenyl-$COOR^7$ wherein R^7 is hydrogen or $(C_1$-$C_4)$alkyl, $(C_0$-$C_4)$alkyl-$COOR^7$, $(C_1$-$C_4)$alkanoyloxy-$(C_2$-

C_4)alkenyl, (C_2-C_4)alkenyl-$CONR^4R^5$ wherein R^4 and R^5 are independently hydrogen, (C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy-(C_1-C_4)alkylene, or (C_3-C_8)cycloalkyl, or R^4 and R^5 taken together with the nitrogen atom to which they are attached form pyrrolidino, piperidino, morpholino, or hexamethyleneimino, (C_0-C_4)alkyl-$CONR^4R^5$, (C_0-C_4)alkyl-NR^4R^5, $OCH_2CH_2NR^8R^9$ wherein R^8 and R^9 are independently methyl or ethyl, or R^8 and R^9 taken together with the nitrogen atom to which they are attached form pyrrolidino, piperidino, morpholino, or hexamethyleneimino, propyl-R^8R^9, and SO_2-R^6 wherein R^6 is imidazolyl, thienyl, benzathienyl, or isoxazyl, optionally substituted with up to three substituents independently selected from (C_1-C_4)alkyl;

X is (C_0-C_1)alkylene-phenylene-(C_0-C_1)alkylene, CO_2, CO, (C_1-C_3)alkylene-CO-(C_1-C_3)alkylene, (C_0-C_3)alkylene-CO-(C_2-C_3)alkylene, (C_2-C_3)alkylene-CO-(C_0-C_3)alkylene, or (C_0-C_4)alkylene-SO_2-(C_0-C_4)alkylene;

R^2 is (C_1-C_9)alkyl; (C_2-C_4)alkenyl; benzhydryl; a partially saturated, fully saturated, or fully unsaturated three to eight membered ring optionally having up to four heteroatoms selected independently from oxygen, sulfur, and nitrogen; a bicyclic ring consisting of two fused independently partially saturated, fully saturated, or fully unsaturated five to six membered rings, wherein said bicyclic ring includes up to four heteroatoms independently selected from oxygen, sulfur, and nitrogen; or a bicyclic ring system consisting of two rings joined by a covalent bond, said rings being independently partially saturated, fully saturated, or fully unsaturated three to eight membered rings, wherein said bicyclic ring system includes up to four heteroatoms independently selected from oxygen, sulfur, and nitrogen; wherein said (C_1-C_9)alkyl is optionally substituted with one to seven fluoro substituents, or up to three substituents independently selected from Group B, wherein Group B consists of chloro, (C_1-C_4)alkoxy, amino, and (C_1-C_4)alkylcarbonyl; wherein said (C_2-C_4)alkenyl is optionally substituted with up to three substituents independently selected from Group C, wherein Group C consists of halo, (C_1-C_4)alkoxy, amino, and (C_1-C_4)alkylcarbonyl; and wherein said benzhydryl, said 5 to 8 membered ring, said bicyclic ring, and said bicyclic ring system is optionally substituted with up to three substituents independently selected from Group D, wherein Group D consists of halo, hydroxy, (C_1-C_4)alkyl, (C_1-

C_4)alkoxy, imidazolyl, amino, (C_1-C_4)alkylcarbonylamino, and (C_1-C_4)alkylcarbonyl; and

p is 0, 1, or 2.

45. A method for treating or preventing a disease, disorder, condition, or symptom mediated by an estrogen receptor and/or caused by lowered estrogen level in a mammal, said method comprising administering to said mammal a therapeutically effective amount of a compound of claim 1.

46. A method according to claim 45 wherein said disease, disorder, condition, or symptom is perimenopausal or postmenopausal syndrome, osteoporosis, atrophy of skin or vagina, elevated serum cholesterol levels, cardiovascular disease, Alzheimer's disease, a reduction or prevention of reduction in cognitive function, an estrogen dependent cancer, breast or uterus cancer, a prostatic disease, benign prostatic hyperplasia, or prostate cancer.

47. A method according to claim 45 wherein said disease, disorder, condition, or symptom is obesity, endometriosis, bone loss, uterine fibrosis, aortal smooth muscle cell proliferation, lack of birth control, acne, hirsutism, dysfunctional uterine bleeding, dysmenorrehea, male infertility, impotence, psychological and behavioral symptoms during menstruation, ulcerative mucositis, uterine fibroid disease, restenosis, atherosclerosis, musculoaponeurotic fibromatosis, alopecia, wound-healing, scarring, auto immune disease, cartilage degeneration, delayed puberty, demyelinating disease, dysmyelinating disease, hypoglycemia, lupus erythematosus, myocardial infarction, ischemia, thromboembolic disorder, obsessive compulsive disorder, ovarian dysgenesis, post menopausal CNS disorder, pulmonary hypertension, reperfusion damage, resistant neoplasm, rheumatoid arthritis, seborrhea, sexual precocity, thyroiditis, Turner's syndrome, or hyperlipidemia.

48. A method according to claim 45 useful for blocking a calcium channel, inhibiting an environmental estrogen, minimizing the uterotropic effect of tamoxifen or an analog thereof, removing fibrin by inhibiting plasminogen activators, inhibiting estrogen positive primary tumors of the brain and CNS, increasing sphincter competence, increasing libido, inhibiting fertility, oxidizing low density lipoprotein,

increasing macrophage function, expressing thrombomodulin, or increasing levels of endogenous growth hormone.

49. A method for treating or preventing a disease, disorder, condition, or symptom mediated by an estrogen receptor and/or caused by lowered estrogen level in a mammal, said method comprising administering to said mammal a therapeutically effective amount of a compound of claim 1 and an amount of an anabolic agent, a prodrug thereof, or a pharmaceutically acceptable salt of said anabolic agent or said prodrug.

50. A method according to claim 49 wherein said disease, disorder, condition, or symptom is perimenopausal or postmenopausal syndrome, osteoporosis, atrophy of skin or vagina, elevated serum cholesterol levels, cardiovascular disease, Alzheimer's disease, a reduction or prevention of reduction in cognitive function, an estrogen dependent cancer, breast or uterus cancer, a prostatic disease, benign prostatic hyperplasia, or prostate cancer.

51. A method according to claim 49 wherein said disease, disorder, condition, or symptom is obesity, endometriosis, bone loss, uterine fibrosis, aortal smooth muscle cell proliferation, lack of birth control, acne, hirsutism, dysfunctional uterine bleeding, dysmenorrehea, male infertility, impotence, psychological and behavioral symptoms during menstruation, ulcerative mucositis, uterine fibroid disease, restenosis, atherosclerosis, musculoaponeurotic fibromatosis, alopecia, wound-healing, scarring, auto immune disease, cartilage degeneration, delayed puberty, demyelinating disease, dysmyelinating disease, hypoglycemia, lupus erythematosus, myocardial infarction, ischemia, thromboembolic disorder, obessive compulsive disorder, ovarian dysgenesis, post menopausal CNS disorder, pulmonary hypertension, reperfusion damage, resistant neoplasm, rheumatoid arthritis, seborrhea, sexual precocity, thyroiditis, Turner's syndrome, or hyperlipidemia.

52. A method according to claim 49 useful for blocking a calcium channel, inhibiting an environmental estrogen, minimizing the uterotropic effect of tamoxifen or an analog thereof, removing fibrin by inhibiting plasminogen activators, inhibiting estrogen positive primary tumors of the brain and CNS, increasing sphincter

competence, increasing libido, inhibiting fertility, oxidizing low density lipoprotein, increasing macrophage function, expressing thrombomodulin, or increasing levels of endogenous growth hormone.

53. A method for treating or preventing a disease, disorder, condition, or symptom mediated by an estrogen receptor and/or caused by lowered estrogen level in a mammal, said method comprising administering to said mammal a therapeutically effective amount of a compound of claim 1 and an amount of growth hormone or a growth hormone secretagogue, a prodrug thereof, or a pharmaceutically acceptable salt of said growth hormone secretagogue or said prodrug.

54. A method according to claim 53 wherein said disease, disorder, condition, or symptom is perimenopausal or postmenopausal syndrome, osteoporosis, atrophy of skin or vagina, elevated serum cholesterol levels, cardiovascular disease, Alzheimer's disease, a reduction or prevention of reduction in cognitive function, an estrogen dependent cancer, breast or uterus cancer, a prostatic disease, benign prostatic hyperplasia, or prostate cancer.

55. A method according to claim 53 wherein said disease, disorder, condition, or symptom is obesity, endometriosis, bone loss, uterine fibrosis, aortal smooth muscle cell proliferation, lack of birth control, acne, hirsutism, dysfunctional uterine bleeding, dysmenorrehea, male infertility, impotence, psychological and behavioral symptoms during menstruation, ulcerative mucositis, uterine fibroid disease, restenosis, atherosclerosis, musculoaponeurotic fibromatosis, alopecia, wound-healing, scarring, auto immune disease, cartilage degeneration, delayed puberty, demyelinating disease, dysmyelinating disease, hypoglycemia, lupus erythematosus, myocardial infarction, ischemia, thromboembolic disorder, obessive compulsive disorder, ovarian dysgenesis, post menopausal CNS disorder, pulmonary hypertension, reperfusion damage, resistant neoplasm, rheumatoid arthritis, seborrhea, sexual precocity, thyroiditis, Turner's syndrome, or hyperlipidemia.

56. A method of claim 53 useful for blocking a calcium channel, inhibiting an environmental estrogen, minimizing the uterotropic effect of tamoxifen or an

analog thereof, removing fibrin by inhibiting plasminogen activators, inhibiting estrogen positive primary tumors of the brain and CNS, increasing sphincter competence, increasing libido, inhibiting fertility, oxidizing low density lipoprotein, increasing macrophage function, expressing thrombomodulin, or increasing levels of endogenous growth hormone.

57. A method for treating or preventing a disease, disorder, condition, or symptom mediated by an estrogen receptor and/or caused by lowered estrogen level in a mammal, said method comprising administering to said mammal a therapeutically effective amount of a compound of claim 1 and an amount of a second compound comprising a prostaglandin agonist/antagonist, a prodrug thereof, or a pharmaceutically acceptable salt of said prostaglandin agonist/antagonist or said prodrug.

58. A method according to claim 57 wherein said disease, disorder, condition, or symptom is perimenopausal or postmenopausal syndrome, osteoporosis, atrophy of skin or vagina, elevated serum cholesterol levels, cardiovascular disease, Alzheimer's disease, a reduction or prevention of reduction in cognitive function, an estrogen dependent cancer, breast or uterus cancer, a prostatic disease, benign prostatic hyperplasia, or prostate cancer.

59. A method according to claim 57 wherein said disease, disorder, condition, or symptom is obesity, endometriosis, bone loss, uterine fibrosis, aortal smooth muscle cell proliferation, lack of birth control, acne, hirsutism, dysfunctional uterine bleeding, dysmenorrehea, male infertility, impotence, psychological and behavioral symptoms during menstruation, ulcerative mucositis, uterine fibroid disease, restenosis, atherosclerosis, musculoaponeurotic fibromatosis, alopecia, wound-healing, scarring, auto immune disease, cartilage degeneration, delayed puberty, demyelinating disease, dysmyelinating disease, hypoglycemia, lupus erythematosus, myocardial infarction, ischemia, thromboembolic disorder, obessive compulsive disorder, ovarian dysgenesis, post menopausal CNS disorder, pulmonary hypertension, reperfusion damage, resistant neoplasm, rheumatoid arthritis, seborrhea, sexual precocity, thyroiditis, Turner's syndrome, or hyperlipidemia.

60. A method according to claim 57 useful for blocking a calcium channel, inhibiting an environmental estrogen, minimizing the uterotropic effect of tamoxifen or an analog thereof, removing fibrin by inhibiting plasminogen activators, inhibiting estrogen positive primary tumors of the brain and CNS, increasing sphincter competence, increasing libido, inhibiting fertility, oxidizing low density lipoprotein, increasing macrophage function, expressing thrombomodulin, or increasing levels of endogenous growth hormone.

61. A method for treating or preventing a disease, disorder, condition, or symptom mediated by an estrogen receptor and/or caused by lowered estrogen level in a mammal, said method comprising administering to said mammal a therapeutically effective amount of a compound of claim 1 and an amount of a second compound comprising parathyroid hormone or sodium fluoride.

62. A method according to claim 61 wherein said disease, disorder, condition, or symptom is perimenopausal or postmenopausal syndrome, osteoporosis, atrophy of skin or vagina, elevated serum cholesterol levels, cardiovascular disease, Alzheimer's disease, a reduction or prevention of reduction in cognitive function, an estrogen dependent cancer, breast or uterus cancer, a prostatic disease, benign prostatic hyperplasia, or prostate cancer.

63. A method according to claim 61 wherein said disease, disorder, condition, or symptom is obesity, endometriosis, bone loss, uterine fibrosis, aortal smooth muscle cell proliferation, lack of birth control, acne, hirsutism, dysfunctional uterine bleeding, dysmenorrehea, male infertility, impotence, psychological and behavioral symptoms during menstruation, ulcerative mucositis, uterine fibroid disease, restenosis, atherosclerosis, musculoaponeurotic fibromatosis, alopecia, wound-healing, scarring, auto immune disease, cartilage degeneration, delayed puberty, demyelinating disease, dysmyelinating disease, hypoglycemia, lupus erythematosus, myocardial infarction, ischemia, thromboembolic disorder, obessive compulsive disorder, ovarian dysgenesis, post menopausal CNS disorder, pulmonary hypertension, reperfusion damage, resistant neoplasm, rheumatoid arthritis, seborrhea, sexual precocity, thyroiditis, Turner's syndrome, or hyperlipidemia.

64. A method according to claim 61 useful for blocking a calcium channel, inhibiting an environmental estrogen, minimizing the uterotropic effect of tamoxifen or an analog thereof, removing fibrin by inhibiting plasminogen activators, inhibiting estrogen positive primary tumors of the brain and CNS, increasing sphincter competence, increasing libido, inhibiting fertility, oxidizing low density lipoprotein, increasing macrophage function, expressing thrombomodulin, or increasing levels of endogenous growth hormone.

65. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable vehicle, carrier, or diluent.

66. A pharmaceutical composition comprising a compound of claim 44 and a pharmaceutically acceptable vehicle, carrier, or diluent.

67. A pharmaceutical composition comprising:

a compound of claim 1;

an anabolic agent, a prodrug thereof, or a pharmaceutically acceptable salt of said anabolic agent or a said prodrug; and

a pharmaceutically acceptable vehicle, carrier, or diluent.

68. A pharmaceutical composition comprising:

a compound of claim 1;

growth hormone, a growth hormone secretagogue, a prodrug thereof, or a pharmaceutically acceptable salt of said growth hormone secretagogue or a said prodrug; and

a pharmaceutically acceptable vehicle, carrier, or diluent.

69. A pharmaceutical composition comprising:

a compound of claim 1;

a prostaglandin agonist/antagonist, a prodrug thereof, or a pharmaceutically acceptable salt of said prostaglandin agonist/antagonist or a said prodrug; and

a pharmaceutically acceptable vehicle, carrier, or diluent.

70. A pharmaceutical composition comprising:

a compound of claim 1;

parathyroid hormone or sodium fluoride; and

a pharmaceutically acceptable vehicle, carrier, or diluent.

71. A kit useful for treating or preventing a disease, disorder, condition, or symptom mediated by an estrogen receptor and/or caused by lowered estrogen levels, said kit comprising:

a compound of claim 1 and a pharmaceutically acceptable vehicle, carrier, or diluent in a dosage form; and

a container for containing said dosage form.

72. A kit useful for treating or preventing a disease, disorder, condition, or symptom mediated by an estrogen receptor and/or caused by lowered estrogen levels, said kit comprising:

a compound of claim 1 and a pharmaceutically acceptable vehicle, carrier, or diluent in a first unit dosage form;

an anabolic agent, a prodrug thereof, or a pharmaceutically acceptable salt of said anabolic agent or said prodrug and a pharmaceutically acceptable vehicle, carrier, or diluent in a second unit dosage form; and

a container for containing said first and second unit dosage forms.

73. A kit useful for treating or preventing a disease, disorder, condition, or symptom mediated by an estrogen receptor and/or caused by lowered estrogen levels, said kit comprising:

a compound of claim 1 and a pharmaceutically acceptable vehicle, carrier, or diluent in a first unit dosage form;

growth hormone or a growth hormone secretagogue, a prodrug thereof, or a pharmaceutically acceptable salt of said growth hormone secretagogue or said prodrug and a pharmaceutically acceptable vehicle, carrier, or diluent in a second unit dosage form; and

a container for containing said first and second unit dosage forms.

74. A kit useful for treating or preventing a disease, disorder, condition, or symptom mediated by an estrogen receptor and/or caused by lowered estrogen levels, said kit comprising:

a compound of claim 1 and a pharmaceutically acceptable vehicle, carrier, or diluent in a first unit dosage form;

a prostaglandin agonist/antagonist, a prodrug thereof, or a pharmaceutically acceptable salt of said prostaglandin agonist/antagonist or said prodrug and a pharmaceutically acceptable vehicle, carrier, or diluent in a second unit dosage form; and

a container for containing said first and second unit dosage forms.

75. A kit useful for treating or preventing a disease, disorder, condition, or symptom mediated by an estrogen receptor and/or caused by lowered estrogen levels, said kit comprising:

a compound of claim 1 and a pharmaceutically acceptable vehicle, carrier, or diluent in a first unit dosage form;

parathyroid hormone or sodium fluoride and a pharmaceutically acceptable vehicle, carrier, or diluent in a second unit dosage form; and

a container for containing said first and second unit dosage forms.